GRIP (GLOBAL HEALTH RESEARCH INITIATIVE PROGRAM FOR NEW FOREIGN INVESTIGATORS) Recipients as of January, 2005

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Grant:	5R01TW006230-03	
Program Director:	PRIMACK, ARON	
Principal Investigator:	AGOT, KAWANGO E	PHD
Title:	Widow inheritance and HIV infection in Kenya	
Institution:	UNIVERSITY OF NAIROBI	NAIROBI,
Project Period:	2002/09/24-2007/06/30	

DESCRIPTION (provided by applicant) We propose to conduct a prospective cohort study to investigate the association between widow inheritance and HIV infection among the Luo ethnic community in Kenya--the community with the highest HIV prevalence in the country. The specific aims of the study are to: 1) assess the association between widow inheritance and acquisition of HIV; 2) examine the relationship between HIV infection and being inherited by a brother-in-law versus by a 'professional'inheritor; 3) evaluate the difference in HIV risk associated with being inherited for companionship and support versus for sexual cleansing; and 4) identify correlates of inheritance overall, as well as of the different types of the practice. To achieve these aims, we will recruit 992 widows through radio announcements; women's, widow's and church groups; fliers, posters and brochures; health talks in clinics; chiefs'community meetings; and Focus Group Discussions with widows. At visit 1, those who consent will be counseled and tested for HIV. Those seronegative and are willing to join the study will come for visit 2 when they will be interviewed on their sociodemographic characteristics, sexual behavior, and medical history. They will also provide blood specimens for gonorrhoea, HSV-2, syphilis, and trichomonas virginals tests. Swabs will be taken from those with genital ulcers to test for haemophillus ducreyi. They will then be followed up quarterly for 24 months, during which time the activities performed at enrolment will be repeated. Exposure will be inheritance, including the different types of the practice, while the main outcome will be HIV seroconversion rate and the secondary outcomes will be the incidence of the various types of STIs. We shall use Epi-lnfo software to enter data and to perform crude and adjusted ManteI-Haenszel tests to obtain the relative risk of acquiring HIV and STI given that a widow is inherited relative to those not inherited. Logistic regression analysis will be used to identify which characteristics are independently related to inheritance. The findings will be the first scientific study of this association and will help in designing HIV intervention programs that are informed by research.

Grant:	1R01TW006970-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	ALEMAN, ALICIA	MD
Title:	Antenatal Corticosteroids in Latin American Countries	
Institution:	UNIVERSITY OF THE REPUBLIC	MONTEVIDEO,
Project Period:	2004/07/01-2008/06/30	

DESCRIPTION (provided by applicant): Preterm birth occurs in 10% of all deliveries but accounts for 74% of neonatal mortality. In relation to this problem, one of the most effective practices, with a high impact in perinatal public health, is the use of antenatal corticosteroids. Although well documented and consistent high quality evidence has demonstrated its effectiveness in preventing morbidity and mortality among premature infants, it remains underused, mainly in developing counties. The general objective of this project is to evaluate the magnitude, characteristics and barriers for the administration of antenatal corticosteroids to women delivering preterm in Latin American countries. The result of this study will enable a long term goal of promoting a wider use of this practice in the region with the subsequent decrease in the neonatal morbidity and mortality. This proposal is a multi-center prospective cross-sectional and descriptive research whose specific aims are: to determine the prevalence and characteristics of administration of antenatal corticosteroids to women who deliver preterm in the hospitals of Latin American countries and to assess the knowledge, attitudes, practices and barriers of the health care providers for the use of antenatal corticosteroids in women at risk of preterm birth in the same region. To achieve the first aim the methodology will be a prospective survey of 1800 women who delivered preterm in hospitals in three Latin American countries (Uruguay, Ecuador and El Salvador). For the second aim, both quantitative and qualitative data will be analyzed. Quantitative data will be collected through self-administered surveys of obstetric providers. Qualitative data will be collected through a series of focus groups. The environment for this research will be the Network of Association Centers to the Latin American Center for Perinatology and Human Development (CLAP/PAHO/WHO). This network of hospitals in Latin American countries was created to improve epidemiological survey, to promote clinical research in the region, to provide teetmical support to other centers and to train health personnel.

Grant: 1R01TW006612-01

Program Director: PRIMACK, ARON

Principal Investigator: ANDRADE, MARCUS V MD

Title: Mast cell toll-like receptors and parasitic pathogens

Institution: UNIVERSIDADE FEDERAL DE MINAS GERAIS BELO HORIZONTE,

Project Period: 2004/02/04-2009/01/31

DESCRIPTION (provided by applicant) The project has three aims: 1) To determine whether or not glycolipids from Leishmania sp (L.sp.) and Trypanosoma cruzi (TC) activate mast cells (MC) through Toll-like receptors (TLR); 2) identify the TLR activated (most likely TLR2), the signaling pathways activated, and the biological responses of MC to these glycolipids; and 3) examine the role of MC in the immunological/pathological reactions to infection from the above organisms in a mouse model. A subsidiary theme is to evaluate the MC as a model for a) studies of the effect of drugs on TLR-mediated responses and b) for identifying other parasite components that act through TLRs. MC are an important component of the innate immune system and are now thought to be essential for elimination of parasite infestation but the mechanism is undefined. Recent reports indicate that MC express TLR2, 4, 6, and 8 which can be activated by bacterial glycolipids via TLR2 to induce production of inflammatory cytokines and degranulation: and via TLR4 to induce production of cytokines but not degranulation. Glycolipids from T.C. also activate TLR2 on macrophages but have yet to be tested on MC. The question we address is whether TLRs are the "recognition" receptors that allow MC to participate in parasite elimination through release of inflammatory mediators. The core signaling pathway activated via TLR2 and TLR4 has been identified but many questions remain, especially so for MC, on how TLR activation leads to gene expression for cytokine production and other biological responses. For aims 1 & 2, studies will be conducted with MC lines as well as cultured bone marrow-derived MC from TLR2- and TLR4- knockout mice. Purified glycolipid components from L.sp. and T.C. will be evaluated for potency along with bacterial glycolipids that activate specifically TLR2 or TLR4. Known TLR-signaling pathways will be examined along with pathways that are responsible for degranulation and cytokine production in antigen-stimulated MC. Dexamethasone will be used as a prototype drug to examine effects on TLR-mediated signals as this drug disrupts several key signaling events in antigen-stimulated MC. For aim 3, normal, mast cell-deficient and TLR-deficient mice will be used to evaluate host responses to L.sp. and T.C. infection using experimental models that are well established in our institution.

Grant:	5R01TW006216-03
Program Director:	PRIMACK, ARON
Principal Investigator:	ARAUJO, MARIA L MD
Title:	Association Between Asthma and Helminthic Infections
Institution:	FEDERAL UNIVERSITY OF BAHIA SALVADOR,
Project Period:	2002/09/18-2005/06/30

DESCRIPTION (provided by applicant) The main hypothesis of this proposal is that parasites play a role in preventing the development of skin prick test reaction to aeroallergens and decreases asthma severity. Helminthic infections are highly prevalent in the world and many infected people are also additionally exposed to other infections and diseases, therefore, this project proposes to evaluate whether helminthic infections down regulate the immune response of allergic diseases resulting in less severe form of asthma and absence of skin prick test response to aeroallergens. The specific aims are: 1. To determine if infections by helminthes interfere with asthma severity. To address this goal at the start of the study and every 2 months during the follow-up year, in infected and uninfected asthmatic subjects, it will be used a questionnaire to evaluate asthma severity, as well as perform a peak flow test and pulmonary function test; 2. To determine the mite fauna and mite allergen levels in house dust samples. To address this goal dust samples from patients house will be collected and evaluated to mite; 3. To both, compare the immune response of asthmatic patients infected by helminthes with uninfected asthmatic patients, and to evaluate the role of IL-10 in regulating this immune response. To address this aim we will perform PBMC culture stimulated with Dermatophagoides pteronyssinus (Der p 1) in the presence or absence of rhlL-10 and evaluate: histamine release, basophil activation and type 1 and type 2 cytokine production. A controlled study of asthma severity and the mechanism by which atopic patients, living in endemic areas of helminthic infections do not respond to the skin prick test to aeroauergens, could lead to the development of new perspectives of prevention and therapy for both asthma and helminthic infections.

Grant: 5R01TW006626-02

Program Director: PRIMACK, ARON

Principal Investigator: BEBENEK, ANNA PHD

Title: Fidelity studies of RB69 DNA Polymerase Mutants.

Institution: POLISH ACADEMY OF SCIENCES WARSAW,

Project Period: 2003/09/30-2006/03/31

DESCRIPTION (provided by applicant): Replicative DNA polymerases are the main determinants of the accuracy of DNA replication and thus of the incidence of heritable birth defects and mutation-primed diseases such as cancer. It is therefore of particular interest to us to understand the mechanism by which the main eukaryotic replicative polymerases achieve high fidelity. Bacteriophage RB69 encodes a replicative DNA polymerase with associated 3"-5" proofreading activity. Like T4 DNA polymerase and many polymerases from archaeons, the RB69 DNA polymerase is a member of the B family which includes the eukaryotic DNA polymerases alpha, delta, and epsilon. The availability of crystallographic structures for this polymerase in both the apo for and the replicating complex makes it an excellent model for structure-function studies. Efficient mutation reporter systems are available both in vivo and in vitro to assess the impact on polymerase accuracy of changes in polymerase residues. To conduct fidelity analyses in vivo, we will use a hybrid system in which T4 DNA replication is driven by a RB69 DNA polymerase. T4 whose DNA polymerase has been mutationally inactivated can be replicated by a cognate RB69 DNA polymerase encoded by a recombinant plasmid in T4-infected Escherichia coil Mutation frequencies are measured using two T4 reporter systems, reversion at the r/I locus, and forward mutation at the rl locus followed by sequencing. These assays provide rapid and sensitive measurements of the mutational specificities of derivatives of RB69 enzyme. To measure fidelity in vitro, we will use the M13mp2 lacZalpha system. This is a gap-filling assay that measures the accuracy of DNA synthesis across a single stranded gap in bacteriophage M13mp2 RF DNA. The gap contains the mutation-reporter lacZalpha as a template. This system detects specific mispairs, and can support measurements of polymerase processivity the role of accessory proteins. In our fidelity studies we will focus first on the highly conserved thumb-domain motif KKRY which contacts primer-template DNA along the minor-groove and is likely to play an essential role in DNA binding and in accurate, processive DNA replication.

Grant:	5R01TW006218-02
Program Director:	PRIMACK, ARON
Principal Investigator:	BURBANO, XIMENA L MD
Title:	IMPACT OF DELIVERY MODELS IN HIV HEALTH CARE IN BOGOTA
Institution:	FUNDACION SANTA FE DE BOGOTA BOGOTA,
Project Period:	2003/09/30-2006/03/31

DESCRIPTION (provided by applicant): Colombia, which ranks fourth in the total number of HIV reported cases in Latin America, implemented a law in 993 to guarantee basic medical care for HIV-infected people. In 1997, provision of antiretrovirals was nandated. Health Services Providers have designed different Delivery Health Care Models to provide ;overage for HIV infected patients. The proposed health research initiative, by a new foreign investigator, will evaluate for the first time, the utilization and cost implications of different representative delivery health care models in Bogota, Colombia. Assessment of cost-effectiveness is vital not only in the area of treatment but also in regard to the use of diagnostics, provision of care, support services, and prevention strategies and programs. A multi-step evaluation of three main Delivery Health Care Models (Open Pre-Paid, EPS, Social Security) available in Bogota, is proposed. First, information will be obtained to determine the type of specific services available for each delivery model. Second, data obtained from 450 HIV-infected individuals (150/model) will be systematically collected and prepared for statistical analysis. In the third phase, models will be compared in terms of health services utilization, costs, cost-effectiveness and which health care model best accomplishes delivery and sustains adherence to HAART. Evaluation of service utilization will consider the impact on disease progression, as indicated by CD4 cell count and viral burden. Outcomes will be aggregated to determine the level of total services required for adequate care for each delivery model. In the proposed research application, the Miami Fogarty Group will provide appropriate resources and guidance to Dr. Burbano, the new foreign investigator, for the implementation of the study, including expertise in health care services and evaluation, research methodology, quality control, data management and data analyses. It is expected that the conduct of this study will advance Dr. Burbano's ability to become a scientific leader in health research. Findings from this project should provide necessary information to help determine the optimal use of HIV delivery services and help develop public health strategies to achieve equity in health services, for HIV infected people in Colombia, and possibly other countries in Latin America.

Grant: 1R01TW006636-01

Program Director: PRIMACK, ARON

Principal Investigator: CABA, MARIO PHD

Title: Ontogenetic Changes in Control of Rhythmicity in rabbits

Institution: UNIVERSITY OF VERACRUZ JALAPA,

Project Period: 2004/03/12-2009/02/28

DESCRIPTION (provided by applicant) Maternal behavior in the rabbit is unusual among mammals. Shortly after parturition the doe leaves the litter and returns around 24 hours later to nurse their pups during 3-5 minutes every day. Chronobiological studies demonstrates that the suckling cycle of the pup is a circadian rhythm as they shows food anticipatory activity before the arrival of the mother. This animal model represents an extraordinary opportunity to study the ontogeny of circadian rhytms with minimal disturbance of the dyad, as mother and young come together once a day for a period lasting only a few minutes. The principal objective of this proposal is to study the anatomy and physiological development of the Suprachiasmatic Nucleus (SCN) of the rabbit when the mother is the principal zeitgeber for the pups. Our final goal is to look for changes in the SCN and extra SCN-forebrain structures in response to changes in timing of the nursing bout and to compare with those induced by light considering that first the mother is the principal zeitgeber and then there is a shift to a light controlled oscillator. The specific aims are: I: Neurogenesis in the Suprachiasmatic Nucleus II: Development of the Retinohypothalamic tract of rabbit pups III: To determine the ontogeny of a photic response in the suprachiasmatic nucleus by ligth-induction of the FOS protein in the SCN and to determine the peptidergic identity of the light-induced cells. IV: To determine the ontogeny of expression of PER1, PER2 and PER3 proteins in the SCN and extra-SCN forebrain structures at PD1, PD7, PD15 and PD20 in LID condition and in response to a light pulse. For all Aims we will use immunocytochemical techniques with specific antibodies. For Aim I we will inject BrdU i.p. to pregnant does from embryonic day 9-30. Pups will be sacrificed at PD1 to determine the day of birth of cells. For Aim II we will inject Cholera Toxin B in the humor vitreous and subjects will be sacrificed 48 h later. For aim III pups will be exposed for 30 min to a light pulse (800 lux) during subjective night and will be sacrificed 60 min later. For Aim IV pups will be scheduled to suckle at different time points, sacrificed every 4 hours around time of suckling in L/D and after a light pulse during subjective night. In this aim the hypothesis is that there is a shift from a food contolled circadian rhythmicity to a light controlled circadian rhythmicity. This research aims to identify and characterize pacemaker cells of the SCN and other brain regions that regulate circadian disorders, e.g. jet lag, shift work. Once characterized, we can use this information to control circadian rhythms in circumstances where it is disrupted.

Grant:	1R01TW007256-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	CHAN, SAU MAN S	MOTH
Title:	Cerebrovascular risk factors and late-life suicide	
Institution:	CHINESE UNIVERSITY OF HONG KONG	TAI PO NEW TERRITORIES,
Project Period:	2005/07/01-2008/06/30	

DESCRIPTION (provided by applicant): The long-term goal of our work is to develop and test suicide prevention measures that are efficient and effective for use in the elderly. Knowledge of the factors that place elders at risk for suicide is necessary for us to reach that goal. A number of medical, psychological and social influences have been shown to be correlates of suicide in late-life. New evidence is emerging to substantiate the effect of a specific domain of medical factors, i.e. cerebrovascular risk factors (CVRFs), on late-life psychiatric disorders, which in turn have already been shown to be robust risk factors for late-life suicide. The primary objective of our study is to examine using a case-control design whether CVRFs at clinical and radiopathological levels independently increase risk of late-life suicide. In our secondary objectives, we will examine the correlation between clinical CVRFs and radiopathological CVRFs. Also, we Will explore whether CVRFs (both clinical and radiopathological) render some at-risk older adults even more vulnerable to self-destruction by way of impaired executive cognitive function (ECF). Cross-sectional case-control design will be employed. 100 cases will be recruited from suicide attempters, ages 65 or over presenting consecutively to a tertiary care setting over a 30-month period; while the same number of controls, of comparable age and sex distribution, without life-time history of suicide, will be recruited from community dwelling elders who attend local elderly recreational centres. Measures of sociodemographic background, suicide behavior profile, psychopathology, personality, physical health profile including clinical cerebrovascular risk factor (CVRFs) and vascular pathologies in MRI of Brain, executive cognitve function and global cognitive function will be administered to all subjects. Logistic regression model will be used to test if there is greater burden of CVRFs at clinical/ radiopathological levels in suicide attempters over controls, after controlling for other biopsychosocial risk factors of late-life suicidal behavior. The model will also test if there is any significant interaction between personality trait of impulsiveness and impaired ECF in increasing risk of suicidal behavior. The correlation between clinical and radiopathological CVRFs as well as the relationship between burden of CVRFs and impaired ECFs will be worked out by correlation statistics.

Grant:	1R01TW007290-01
Program Director:	PRIMACK, ARON
Principal Investigator:	CHHAGAN, MEERA K MS
Title:	Metabolic and Nutritional Effects of Art in Children
Institution:	NELSON R MANDELA SCHOOL OF MEDICINE CONGELLA 4013,
Project Period:	2005/01/01-2010/11/30

DESCRIPTION (provided by applicant): This study aims to examine the nutritional, metabolic and growth effects of antiretroviral therapy (ART) on children in South Africa, the country with the largest number of children requiring ART in the world. Currently little is known on the effects of ART in children, and what is known comes from industrialized countries, where the malnutrition and infectious co-morbidities so prevalent in African children are often not present. The findings from this study will be important in informing both the clinical management and public health policy of the worldwide initiative to provide ART to the world's HIV-infected children. Specific aims of this study are to: 1) describe growth and body composition changes in the two years following initiation of ART; 2) describe the incidence of metabolic derangements and lipodystrophy in these children and temporal relationship with commencement of ART; 3) describe the relationship between pretreatment nutritional status and drug tolerability/ metabolic abnormalities in the two years after initiation of ART; 4) determine if body composition changes are related to changes in viral load or CD4 percentage; 5) determine predictors of ART failure. We will recruit 150 treatment naive symptomatic prepubertal HIV-infected children who are commencing triple-drug antiretroviral therapy. Study participants will be recruited during the first two yeas of the study, and will be recruited from two sites: the HIV Family Clinic in King Edward VIII Hospital in Durban; and at the Africa Centre/Hlabisa Health sub-District ART program in rural KwaZulu Natal. ART will be provided according to ART guidelines of the KwaZulu Natal Provincial Department of Health (KZN DOH). These guidelines recommend stavudine, lamivudine and lopinavir/ritonavir for children less than 3 years, or stavudine, lamivudine and efavirenz if older than 3. Study participants will be followed monthly initially and then 3 monthly. We will measure attained growth (height and weight), body composition (skinfold thickness and bioimpedance assessment), lipodystrophy (clinical features and skinfold ratio), markers of dyslipidemia and glucose homeostasis, evidence of drug adverse effects and evidence of treatment failure (based on changes in CD4 cell percentage and HIV viral load) at each visit throughout the study. We will use the following statistics to describe growth patterns and frequency of metabolic abnormalities following initiation of ART: means/medians and 95% confidence intervals, bivariate and multivariate logistics regression models to determine the relationship of pretreatment nutritional status, drug tolerability and metabolic abnormalities, and predictors of treatment failure. All data will be entered into Epi Info and will be analyzed using standard PC-based data analysis packages, including SAS and SPSS.

Grant: 1R01TW006977-01

Program Director: PRIMACK, ARON

Principal Investigator: CIANELLI, ROSINA

Title: An HIV/AIDS prevention Intervention for Chilean women

Institution: CATHOLIC UNIVERSITY OF CHILE SANTIAGO,

Project Period: 2004/07/01-2009/06/30

DESCRIPTION (provided by applicant): At present there are no specific HIV/AIDS prevention programs tailored to the needs of Chilean women, despite their unique vulnerability and the increasing numbers infected by HIV. Serious unmet HIV prevention needs, as well as gender inequalities and other barriers to HIV prevention for low-income Chilean women, were identified in the Prs dissertation (Cianelli, 2003). The proposed research builds on this prior work to develop and test an HIV prevention intervention specifically tailored for low-income Chilean women. A combination of qualitative and quantitative methods will be used. In Phase I, qualitative interviews will elicit 3erspectives on HIV prevention of men--who control many aspects of women's lives--and of community leadersention to compliment to the relevant attitudes of Chilean women already identified in the Pl's dissertation research. A new HIV intervention tailored for low-income Chilean women, Mano a Mano (Hand to Hand) will be developed integrating the insights of Chilean women, community leaders and men with two existing HIV prevention interventions shown to be effective in other contexts. A pilot test will be conducted to assess the intervention's acceptability and feasibility. Phase II will assess the effectiveness of the Mano a Mano intervention in increasing HIV prevention behaviors for Chilean women. The intervention should improve participants'knowledge, attitudes, and HIV prevention behaviors. A quasi-experimental design with a comparable control group will be used with assessments made at baseline, immediate post-intervention, and follow up at 6 weeks and 3-months. A sample of 500 women (250 in the intervention group and 250 in the control group) will provide adequate power to test the research hypotheses. Because the intervention is low-cost and uses existing infrastructure, its transfer potential will be high. If the intervention is effective, it can be disseminated for low-income women throughout Chile. To build the Prs capacity as an independent researcher, the coinvestigator/mentor team will provide support throughout the 5-year study.

Grant:	5R01TW006189-03	
Program Director:	PRIMACK, ARON	
Principal Investigator:	DIAZ-CUETO, LAURA	MD
Title:	Acrogranin Function in the Ovary	
Institution:	COORDINACION DE INVESTIGACION EN SALUD	MEXICO CITY,
Project Period:	2002/09/18-2007/06/30	

DESCRIPTION (provided by applicant) Ovarian carcinoma is the fifth most common cause of cancer among women in the USA, with more than 23,000 new cases diagnosed and approximately 14,000 deaths each year. In Mexico, ovarian cancer is the seventh cause of cancer among women. In our hospital, ovarian cancer corresponds to 15% of all the cancers with an average of 100 cases per year. The epithelial ovarian carcinomas, which make up more than 90% of human ovarian cancers, arise in the ovarian surface epithelium. The etiology and early events in the progression of these carcinomas are among the least understood of all major human malignancies, but the majority of evidence suggests that reproductive factors and genetics may play roles in the origin of this disease. Recent studies have demonstrated that a new family of growth factors [epithelin, granulins and acrogranin (the precursor)] have regulatory activities on preimplantation mouse embryo, normal epithelial and tumoral cells in rodents and human, following interesting signal transduction pathways and are over expressed in some kind of human cerebral tumors, renal cell epithelial carcinomas. The objectives of this proposal are determined if acrogranin is expressed in early stages in the embryo and if it has some role in ovarian development in the mouse. In the second aim we want to examine if acrogranin is over expressed in other kinds of epithelial tumors (ovary) and if it is over expression is associated with malignancy. In the third aim will be explored the signal transduction pathway in epithelial ovary cancer cell lines, we consider that acrogranin activate the MAP kinases pathway for stimulate DNA synthesis, and it does not follow the ras pathway in epithelial ovary cancer. The results of the proposed experiments will lead to significant advances in understanding the participation of acrogranin in the pathogenesis and or malignant progression of the cancer at the clinical and molecular levels. A rational design of selective reagents that target the acrogranin pathway should afford new therapeutics targets for human cancer where acrogranin has a role.

Grant:	5R01TW006192-03
Program Director:	PRIMACK, ARON
Principal Investigator:	DIMITROV, PLAMEN S MD
Title:	Balkan Nephropathy: Environmental/Clinical Epidemiology
Institution:	BULGARIA NTL CTR HYGIENE/MED SOFIA, ECOL/NUTR
Project Period:	2002/09/23-2007/06/30

DESCRIPTION (provided by applicant) This application responds to RFA-TW-02-002 "Global Health Research Initiative Program For New Foreign Investigators". The Principal Investigator successfully completed his training under an NIH D43 Program (ITREOH), Number 2 D43 TW00641-06, in May 2001, at Michigan State University (MSU) for a Master's Degree in Epidemiology and research on Balkan Endemic Nephropathy (BEN). The PI returned to his country in May 2001 and presently has an appointment with the National Center of Hygiene, Medical Ecology and Nutrition (NCHMEN), Sofia, Bulgaria. In the NCHMEN, he occupies the position of the Head of Epidemiology Laboratory, and he is entrusted with the task of developing the field of Epidemiology. Currently he continues his research on BEN and publishes extensively. His training at MSU, under NIH 2 D43 TW00641-06, and continuing collaboration with MSU will greatly facilitate his task in developing an epidemiology program (training and research) at the NCHMEN and the greater Sofia, and his BEN research. We propose to conduct research on Balkan Endemic Nephropathy in Vratza district, Bulgaria. BEN is a disease, which affects people only in rural areas in Balkan countries, including Vratza district, Bulgaria. In the region, the disease is still a mystery and risk factors remain putative. There is a need to identify the etiology of the disease in order to possibly prevent its development. BEN runs asymptomatically, and, as a result, it is diagnosed at its latest stages. Diagnostic criteria are not well established. There is a need to identify the clinical development in the early stages of the disease, which will help for timely detection and possibly treatment. The proposed work would provide critical information for early detection and a scientific base for the diagnostic criteria of Balkan Endemic Nephropathy. Through this project, we expect to improve our knowledge about diagnostic criteria and early markers of BEN. Thus, we will contribute to the detection of the disease, which is predominant in women - 2/3 of cases are women. At the environmental level, we will identify whether some natural toxicants present in the environment in the region contribute to the development of BEN, and whether these are associated with any early markers of the disease. The proposed grant would strengthen collaboration between the Principal Investigator and his former U.S. scientific mentors.

Grant:	5R01TW006207-03	
Program Director:	PRIMACK, ARON	
Principal Investigator:	DU, SHUFA	MD
Title:	China Childhood Obesity Survey	
Institution:	CHINESE CTR-DISEASE CONTROL/PREVENTION	BEIJING,
Project Period:	2002/09/18-2007/06/30	

DESCRIPTION (provided by applicant) Childhood obesity is a growing concern--even in developing countries. During the past two decades, the prevalence of these conditions increased alarmingly and has reached epidemic proportions in most countries in which data are available. Our overall goal is to understand the primary determinants of childhood obesity and to provide guidance for future community-level and macro-level programs to prevent and control obesity and other related degenerated diseases. The specific aims of the proposed research are: (1) To explain how environmental factors affect health-related behaviors, childhood obesity and hypertension; (2) To understand how, and why, the prevalence of childhood obesity changes and to test the hypothesis that it decreases as age increases during childhood and early adolescence; (3) To test the hypothesis that stunting increases the risk of obesity. This research will focus on children at age six because our national research data showed the prevalence of obesity was much higher among preschool children and decreased sharply after age six, but increased again at adulthood. Children are the best candidates for interventions to prevent obesity. It is also easier for us to follow them and observe their growth. We propose a longitudinal study of children in two large cities in China (one in southern China and another one in northern China). We introduce a stratified random cluster sampling method to select our sample. Our total sample at the beginning will be 2,000 subjects from 48 primary sample units (PSUs) with extensive variability of community-level exposures. We will construct a longitudinal model. Our goal is to focus on the role of the environmental changes within the model. Our first step is to determine the impacts of past and current environmental factors on dietary behaviors and physical activities. Next, we will focus on how these behavior changes affect childhood obesity and hypertension. We will use standard, mixed-model to estimate the coefficients, and will use bootstrap strategies to estimate the standard error and confidence intervals for the parameters based on the longitudinal models.

Grant: 5R01AI056235-02

Program Director:

Principal Investigator: FATAKI, MAULIDI R MD

Title: Effect of Zinc Supplementation on Pneumonia in Children

Institution: MUHIMBILI UNIVERSITY COLL OF HEALTH DAR ES SALAAM, SCIS

Project Period: 2003/09/15-2006/08/31

DESCRIPTION (provided by applicant) Randomized trials carried out elsewhere in the developing countries have shown that dietary zinc supplementation in apparently healthy children reduces pneumonia incidence by 41%, however, all the studies that were analyzed had looked at the efficacy of zinc supplementation on the incidence of pneumonia during a prospective follow-up period and none had looked at the effect of zinc supplements on an episode of respiratory disease during the course of treatment. We propose to undertake a randomized, double blind, placebo-controlled trial to examine whether daily oral supplement of 10 mg of elemental zinc will reduce severity of respiratory disease among children admitted at Muhimbili National Hospital, Dares Salaam, Tanzania with radiographically confirmed pneumonia. Six hundred children aged between 6 months and 5 years who will be admitted because of radiologically confirmed pneumonia and whose parents/caretakers will give consent will be recruited during a 3-year study period and will be randomly assigned to receive either daily zinc supplements or placebo and the outcome between the two groups will be closely monitored and documented to determine any beneficial effects of zinc supplements on the course of hospital treatment of pneumonia with duration of hospital stay, fever, rapid respiratory rate and hypoxia as endpoints of interest After discharge from hospital each patient will be followed for duration of 6 months, once every month at study clinic at Muhimbili National Hospital to determine the effect of zinc supplements on growth patterns using increment in weight and height as endpoints. Baseline laboratory investigations to determine serum zinc levels, hematological profile and on consent HIV status will be done and a repeat of serum zinc levels will be done at the end of 6 month follow-up period for each child. At the end of the study appropriate statistical tests will be done to analyze the effects between the two study groups and dissemination of the information will be done.

Grant:	5R01TW006197-03	
Program Director:	PRIMACK, ARON	
Principal Investigator:	FERRAND, PEDRO E	MD
Title:	Variation in Cytokine and MMP Genes and Risk of PPROM	
Institution:	UNIVERSITY OF CHILE	SANTIAGO,
Project Period:	2002/09/19-2007/06/30	

DESCRIPTION (provided by applicant) Preterm Premature rupture of the membranes (PPROM) is a major cause of preterm birth and perinatal morbidity/mortality. It has been hypothesized that pro-inflammatory cytokines are important mediators of PPROM. Cytokines induce expression of matrix metalloproteinases (MMPs) that degrade the extracellular matrix, which gives the membranes their tensile strength. We hypothesize that variation in pro-inflammatory cytokine and MMP genes contributes to the risk of PROM and that gene-environment interactions amplify the risk. The long-term goal of this research is to identify genes that make significant contributions to risk of preterm premature rupture of membranes (PPROM) and how infection interacts with these genes to increase the risk of the unfavorable obstetrical outcome. Our specific aim are: 1) To determine if variation in the MMP-7 gene influences risk of PPROM. The hypothesis to be tested is that MMP-7 promoter alleles with stronger activity will be associated/linked with increased risk of PPROM. 2) To determine if variation in the IL-6 gene influences risk of PPROM. The hypothesis to be tested is that alleles that confer greater IL-6 expression will be associated/linked with increased risk of PPROM. 3) To determine if variation in the MMP-8 gene influences risk of PPROM. We will determine if there are polymorphisms in the MMP-8 promoter and if these variants affect MMP-8 promoter activity and influences risk of PPROM. 4) To determine if bacterial vaginosis and maternal or fetal genotype for the IL-6, MMP-7 or MMP-8 genes interact to affect the risk of PPROM. The hypothesis to be tested is that bacterial vaginosis will increase the risk of PPROM when the maternal or fetal genotypes include alleles with the strongest promoter activity. "To address these aims we will conduct allelic association studies using a case-control design. The study population will be recruited from the obstetrical services of the Hospital San Borja Arriaran, Santiago, Chile (over 9,000 deliveries/year). The study will be restricted to Hispanic women, their partners and offspring. If positive results emerge from the association studies, we will examine linkage using the transmission disequilibrium test. Collectively, these studies could provide evidence for the contribution of genetic factors to the risk of preterm birth.

Grant:	5R01NS046094-03	
Program Director:		
Principal Investigator:	FRIDMAN, ESTEBAN A	MD
Title:	Novel brain stimulation to enhance stroke recovery	
Institution:	ARGENTINA INST OF NEUROLOGICAL RESEARCH	BUENOS AIRES,
Project Period:	2002/09/30-2005/08/31	

DESCRIPTION (provided by applicant) This proposal is concerned with recovery of motor function following brain damage after a cerebrovascular infarct. Though functional reorganization has been shown within the premotor cortex following recovery after stroke, we still known relative little about whether these changes can be enhanced during the neurorehabilitative period if special designed techniques, that stimulate the premotor cortex, are applied. Basic research studies have suggested an increase activity of the premotor cortex during conditional motor learning and during reaching and grasping an object. Therefore, we designed a conditional reaching and grasping motor training to indirectly stimulate this area of the brain in stroke patients during the recovery process. Moreover, increases of cortical activity and corticospinal excitability have followed trains of repetitive transcranial magnetic stimulation in humans. Thus, we designed a scheme of repetitive transcranial magnetic stimulation to directly stimulate the premotor cortex in stroke patients during the neurorehabilitative period. The aim of this proposal is to evaluate the efficacy of these two novel stimulation techniques, supported by neural basis, to enhance motor recovery after stroke. We designed two parallel independent prospective, single-blind, randomize, controlled trials in which we will objectively evaluate behavioral and kinematics changes during motor performance and correlate them with neurophysiological analysis. A voluntary reach-retrieval- delivery task that is an important component of the daily life will be used for the assessment. The proposed work promises to contribute important new insight into the field of therapeutic modalities that can be used to increase motor recovery after stroke. In addition, it will provide some insight into mechanisms underlying such recovery. Since stroke is the leading cause of motor disabilities this work has a clear clinical relevance.

Grant:	5R01TW006604-02	
Program Director:	PRIMACK, ARON	
Principal Investigator:	GHOSH, SAURABH	PHD
Title:	STATISTICAL METHODS FOR MAPPING MULTIVARIATE PHENOTYPES	
Institution:	INDIAN STATISTICAL INSTITUTE	KOLKATA 700 108, IN
Project Period:	2003/09/30-2008/03/31	

DESCRIPTION (provided by applicant) The overarching goal of this research proposal is to devise efficient and robust statistical methods for genetic dissection of complex human traits, which are determined by a complex interplay of gene-gene and gene-environment interactions. Our basic tenet is that for the dissection of the determinants of such traits, specifically to map the underlying genes, the study of the precursor variables that modulate an end-point trait is statistically more powerful than studying the end-point trait itself, which is usually dichotomized (affected/unaffected) by defining a threshold on the frequency distribution of a quantitative trait. The major aims of this research are: (i) to develop non-parametric methods including kernel smoothing and quantile based regression techniques for linkage and association mapping multivariate phenotypes (possibly comprising a mixture of quantitative and binary variables) using data on different types of relative-sets and also unrelated individuals. (ii) to compare the proposed distribution-free methods with existing distribution based methods through extensive computer simulations, (ii) to statistically assess the advantages of using SNP markers in haplotype blocks for QTL mapping, (iv) to develop user-friendly computer programs incorporating the methodologies, (v) to modify the proposed methods to incorporate inbreeding practiced in some populations and (vi) to apply the new methods to data on different types of complex traits/disorders in disparate ethnic populations. The major statistical thrust of this research will be on development of distribution-free gene-mapping methodologies for mixed (quantitative and binary) multivariate phenotypes in the presence of epistatic and gene-environment interactions. Our past studies on univariate phenotypes (Ghosh and Majumder, American Journal of Human Genetics, 2000, 66:1046-1061) have shown that this approach is efficient and robust, especially when distributional assumptions (such as, normality) and model assumptions (such as, dominance at the QTL) are not valid.

Grant:	1R01TW007298-01
Program Director:	PRIMACK, ARON
Principal Investigator:	HE, NA PHD
Title:	Community-based VCT for HIV in Rural Migrants in China
Institution:	FUDAN UNIVERSITY SHANGHAI,
Project Period:	2005/05/01-2008/04/30

DESCRIPTION (provided by applicant): The rapidly increasing size of the migrant population floating between rural and urban areas of China during the last two decades while the HIV epidemic has also been rapidly spreading has been a major challenge for the prevention and control of HIV/AIDS in the world's most populous country. A few studies in China have demonstrated that migrants are very likely to engage in risk behaviors that lead to HIV infection. However, very few migrants have ever received HIV testing and counseling, due to the social stigma to HIV/AIDS and risk behaviors, very low awareness of risk of HIV/AIDS, limited access to health services, and paucity of resources. With respect to WHO's statement that knowing one's HIV status is the first step to accessing care and preventing further infection, this study is proposed to mobilize rural migrant communities in urban areas to accept and get access to HIV/AIDS prevention and, in particular, HIV testing and counseling, as well as reduction of behaviors promoting transmission of HIV. The specific aims of the proposed study are to: 1) promote awareness of HIV/AIDS/STDs and healthy behaviors among rural migrants through community mobilization and health education; and 2) evaluate a community-based comprehensive strategy using multiple HIV counseling and testing models. The long-term objective of this study is to provide useful information for Chinese Government to develop effective and feasible HIV prevention and control strategies that are particularly relevant to the vulnerable migrant population in China.

Grant:	1R01CA112020-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	HENDRICKS, DENVER T	PHD
Title:	NDRG1 in squamous cell oesophageal cancer	
Institution:	UNIVERSITY OF CAPE TOWN	OBSERVATORY 7925 SOUTH AFRICA,
Project Period:	2004/09/15-2009/08/31	

DESCRIPTION (provided by applicant): Squamous cell oesophageat cancer (SCOC) occurs with a high frequency in South Africa (13.61/100 000), where it causes the most cancer-related deaths in Black males. A better understanding of the molecular events involved in the development of oesophageal cancer will allow early diagnosis, the development of better therapeutic strategies and the prevention of metastatic spread. The project aim is to determine the role of NDRG1 (N-Myc Downstream Regulated Gene 1) in the development of SCOC, since it was demonstrated that expression of this gene was reduced in poorly differentiated oesophageal tumors. The function of this protein is presently unknown, although there are reports implicating this gene in cell differentiation, cell proliferation and metastasis. The specific aims of the project are determine the role of specific transcriptional factors (c-Jun, HIF-la, N-Myc and c-myc) in regulating the expression of NDRG1 in cultured oesophageal cancer cells by generating stable transfectants, in which the level of these transcriptional factors are altered. NDRG1 expression levels will also be altered in oesophageal cancer cells by placing NDRG1 or anti-sense NDRG1 under the control of an inducible promoter. This system will be used to test the effect of NDRG1 on markers of tumorigenesis (differentiation, cell proliferation, cell migration and invasion, and metastasis). In addition, deletion mutants of NDRG1 will be constructed, and these will be expressed in oesophageal cancer cells. The effect of these deletions on the sub-cellular localization of NDRG1 and markers of tumorigenesis described above will be determined.

Grant:	5R01TW006186-03	
Program Director:	PRIMACK, ARON	
Principal Investigator:	JIN, DONG-YAN	PHD
Title:	Mitotic Checkpoint & Genomic Stability in Ovarian Cancer	
Institution:	UNIVERSITY OF HONG KONG	HONG KONG,
Project Period:	2002/09/18-2007/06/30	

DESCRIPTION (provided by applicant) Ovarian carcinoma is a leading cause of cancer death worldwide among women. The molecular mechanisms of ovarian carcinogenesis are not known, although a role for heredity has been suggested. We have shown recently that defects in the mitotic checkpoint are common in ovarian cancer. The mitotic checkpoint is a conserved surveillance system that prevents anaphase onset until all chromosomes are aligned. Loss of mitotic checkpoint results in genomic instability, which is a hallmark of cancer. However, it is still not fully understood how proteins interact to enforce the mitotic checkpoint. The proposed studies are designed to investigate the molecular basis of mitotic checkpoint in mammalian cells and its relevance to genomic instability in ovarian cancer. Specifically, we will: (a) fully characterize newly identified isoforms of mitotic checkpoint proteins MAD1 and CDH1; (b) study the transcriptional regulation of the expression of checkpoint proteins MAD1 and MAD2; (c) characterize the interaction of MAD1-MAD2 with the nuclear pore complex; and (d) identify the upstream signals regulating MAD2B-CDHI. Our studies will shed light on the integration of mitotic checkpoint functions with the programs of cell proliferation and cell death. In all studies the relevance to ovarian cancer will be assessed. In particular, we will: (a) screen ovarian cancer cells and tissues for loss of heterozygosity and mutations in mitotic checkpoint loci; (b) compare the expression and localization patterns of various mitotic checkpoint proteins in ovarian cancer cells and correlate them with checkpoint stringency and oncogenic potential; (c) investigate the genetic and epigenetic causes of mitotic checkpoint defects in ovarian cancer; and (d) study the anti-proliferative mechanisms of mitotic checkpoint-targeting drugs such as taxol and vincristine using ovarian cancer as a model. We have shown in various systems that MAD2 and other checkpoint proteins sensitize cells to mitotic checkpoint-targeting chemotherapeutic drugs. Further elucidation of the causative roles of checkpoint defects for drug resistance will reveal novel strategies for combination therapy.

Grant:	5R01TW006231-03
Program Director:	PRIMACK, ARON
Principal Investigator:	KANNABIRAN, CHITRA PHD
Title:	RETINITIS PIGMENTOSA IN INDIA: MOLECULAR GENETIC STUDI*
Institution:	HYDERABAD EYE RESEARCH FOUNDATION-L V ANDHRA PRADESH, IN PR
Project Period:	2002/09/20-2005/06/30

DESCRIPTION (provided by applicant) Retinitis pigmentosa (RP) is one of the major forms of blindness worldwide. It is inherited as autosomal dominant, recessive and X-linked disease. It is an important cause of childhood blindness in India, with the autosomal recessive mode of inheritance being the most prevalent in sections of the population, particularly in South India. RP is extremely heterogeneous and the identification of genes causing the disease is an essential step towards the design of therapeutic agents. Recessive RP in India is frequently associated with consanguinity. The goal of this study is to identify the genetic bases for recessive RP in India. This knowledge is expected to contribute towards an understanding of the pathophysiology of RP, and to be of potential use in the genetic counseling of patients. The approach that we plan to employ consists of: a) Screening families with recessive RP for homozygosity by descent at candidate gene loci. Microsatellite markers that flank several genes known to cause dominant and recessive RP as well as other types of retinal dystrophy will be screened for homozygosity in affected offspring versus parents. The presence of homozygosity at a given locus in affected individuals will be interpreted to mean that the locus is possibly segregating with disease and the relevant candidate gene will be screened for mutations, b) Identification of new loci by genome-wide linkage analysis. Families that are negative in the first screening step will be analyzed by genome-wide linkage analysis to identify disease loci. The use of large consanguineous pedigrees will facilitate this approach. Identified loci will be screened for potential candidate genes within that interval. Possible candidate genes will be analyzed for: 1) Expression in the retina/RPE 2) Sequence changes associated with disease.

Grant:	5R01TW006640-02
Program Director:	PRIMACK, ARON
Principal Investigator:	KIARIE, JAMES N MD
Title:	Interventions to reduce HIV-1 incidence after delivery
Institution:	UNIVERSITY OF NAIROBI NAIROBI,
Project Period:	2003/09/30-2006/03/31

DESCRIPTION (provided by applicant): Women in sub-Saharan face a high risk of HIV-1 acquisition during the first year postpartum which can be reduced by antenatal voluntary counseling and testing (VCT) and using female controlled HIV-1 prevention methods. In preventing heterosexual HIV-1 transmission, the success of female controlled methods such as female condoms, the vaginal diaphragm, and vaginal microbicides depends on their use by women at a high risk of HIV-1 infection. In studies of prevention of mother-to-child transmission (PMTCT) little attention has been paid to women identified as HIV-1 negative and their risk of becoming infected after delivery. An understanding of the factors that influence HIV-1 incidence among uninfected mothers, and which female controlled prevention methods are most acceptable to them, is crucial for preventing HIV-1 acquisition in these women, and hence, preventing additional mother-to-child transmission of HIV-1 in future pregnancies. We propose to determine the potential effectiveness of female controlled HIV-1 prevention methods, and the impact of participation in perinatal HIV-1 prevention programs on HIV-1 incidence in the first year after delivery (assessed using a detuned ELISA at 9 to 12 months postpartum) in three sites in Kenya. The specific aims of the study are to: 1. Determine the correlates of incident HIV-1 infection among Kenyan women in the first year postpartum; 2. Compare the incidence of HIV-1 infection among women who have participated in perinatal HIV-1 prevention programs to the incidence among those who have not participated in these programs; 3. Determine women's knowledge, attitudes, and willingness to use vaginal microbicides, the female diaphragm, and female condoms; 4. Estimate the effectiveness of the various HIV-1 prevention methods based on theoretical efficacy, the number and HIV-1 infection risk of women willing to utilize these methods. This study will provide important information on how to increase the effectiveness of female controlled HIV-1 prevention methods by targeting women at a high risk of acquiring HIV-1 infection. The study will also identify ways to increase the impact of antenatal VCT in reducing HIV-1 incidence.

Grant:	5R01TW006212-03
Program Director:	PRIMACK, ARON
Principal Investigator:	KORDON, EDITH C PHD
Title:	Tumor progression and apoptosis in mouse mammary gland
Institution:	NATIONAL ACADEMY OF MEDICINE BUENOS AIRES,
Project Period:	2002/09/23-2007/06/30

DESCRIPTION (provided by applicant) The present project addresses two main goals: 1) Discovering new pathways involved in mammary tumor progression, particularly those related to the loss of hormone-dependency; and 2) determine the events that initiate the cascades that trigger programmed mammary cell death during mammary gland involution. Understanding what determines the neoplastic-cell lack of response to the regulatory controls for cell proliferation and death is the main goal for experimental oncology. In the case of mammary cells, one of the main controls for proliferation and differentiation resides in the action of pregnancy-related hormones. Determine new genes and pathways that release the mammary epithelial cells from such a control is a fundamental issue in the fight against breast cancer. A particular aspect of this process will be focused in our studies: the fast and aggressive behavior of tumors that resume growth after long periods of dormancy. Although a relevant issue in the treatment of cancer patients, there have not been too many cellular or molecular approaches to this issue. Our studies will be carried out using new MMTV variants that induce pregnancy-dependent tumors that progress to a hormone-independent behavior. Using the Inverse PCR technique, the MMTV sequences will provide us a molecular tag for cloning host genomic regions that, when altered, contribute to tumor progression. It has been proposed that stimuli that trigger apoptosis in normal ceils, would fail in neoplastic tissue, the mammary gland, the process by which the lactating gland goes back to a virgin-like state is known as mammary involution. This process takes place after each lactation period and involves a very important reduction, by apoptosis, of the mammary alveolar epithelium. The signaling pathways that become activated in the mammary secretory cells right after weaning have received a lot of attention in the scientific community during the last years. However, the very early causes that determine the initiation of this process remain unknown. The purpose of the experiments described in our project is to study these early events to determine how the lack of suckling induces mammary cell death. This issue will be approached by in rive as well as in vitro experiments. In addition, we will focus in determining whether neoplastic cells show alteration in the signaling pathways that lead to mammary epithelium cell death and whether that would be relevant during tumor progression.

Grant:	1R01TW007241-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	KOVACS, MIHALY	PHD
Title:	Emerging New Types of Motility	
Institution:	EOTVOS LORAND UNIVERSITY	PAZMANY P SETANY 1/A,
Project Period:	2005/09/01-2010/08/31	

DESCRIPTION (provided by investigator): Long-term Objectives: 1. To explore new types of motility within the myosin superfamily; 2. To address fundamental unresolved issues in motor protein biochemistry such as the relation of the powerstroke to the actin binding transitions and product release steps of myosin. Significance: Motility and contractility are essential for almost all biological processes. Detailed quantitative knowledge of the enzymology of molecular motors is a prerequisite for understanding biological motility and the basis of physiological processes connected to, among others, cardiac function and malfunction, asthma, axonal regeneration and sensory illnesses. Specific Aims: 1. We will test the hypothesis that mechanical load has a functionally important effect on the product release kinetics of non-muscle myosin II; 2. We will assess if myosin X, a membrane-associated motor, has a unique mechanism of action that differs from all described types of myosin-based motility; 3. By mutational perturbation of the product release steps of myosin V, we will investigate the relation of product release to the mechanical step (powerstroke) and actin binding transitions of myosin. We will also establish the correspondence between the kinetic effects of the mutations and motility and processivity. Research Design and Methods: We will address the above questions by using single- and double-headed recombinant myosin constructs for solution kinetic, spectroscopic, biochemical and molecular mechanical investigations.

Grant:	1R01AI056319-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	KREKULOVA, LAURA	MD
Title:	Hepatitis C in Central Europe	
Institution:	NUSLE CLINIC	140 00 PRAGUE4,
Project Period:	2003/07/01-2007/12/31	

DESCRIPTION (provided by applicant) This is a reentry grant proposal being submitted by an investigator who has undergone Fogarty International Center (FIC)-supported training at the University of California, Berkeley in molecular epidemiology of viral hepatitis. The study will focus on hepatitis C in Prague, Czech Republic. Hepatitis C is a major emerging infectious disease problem in Central and Eastern Europe, especially among young adults who engage in injection drug use (IDU) practice. IDU practice itself has become an epidemic in the last 10 years in Prague, Czech Republic. We wish to take advantage of this epidemic to characterize the natural history, clinical response to therapy, and epidemiology of hepatitis C in Prague. One unique feature of the current hepatitis C epidemic in Prague is that the hepatitis C viral (HCV) subtype diversity is limited, compared to those cities in the US or Western Europe, where IDU has been in practice for a much longer time. Hence, we wish to determine if any sets of viral strain types can be shown to be associated with adverse clinical outcome and response to antiviral therapy. To do so, we plan to 1) compare prospectively HCV genotype and subtype distribution, and evolution of the viral subtypes among cohorts of IDU and non-IDU subjects undergoing treatment for HCV infection in Prague, and determine if such characteristics are associated with certain treatment outcomes; 2) study the natural history of the HCV epidemic among untreated IDU populations for viral subtype distribution, evolution, and clinical outcomes among newly infected subjects in Czech Republic; and 3) create a registry of a database related to viral strain type, patient clinical characteristics, and therapeutic response rates that may be used to evaluate the long-term consequences of HCV infection (cirrhosis, hepatocellular carcinoma) for future use. In the process, we wish to learn about the epidemiology of hepatitis C in Prague and provide new data that may be ultimately used for designing better intervention strategies, including the identification of new antiviral drug targets and HCV vaccine candidates. We also believe that what we learn in Prague will have relevance to other regions in Central and Eastern Europe, including Russia where similar epidemics of IDU are occurring.

Grant:	1R01TW007255-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	MARTINEZ CALVILLO, SANTIAGO	PHD
Title:	RNA Polymerase III transcription in Leishmania major	
Institution:	NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO	TLALNEPANTLA, EDO DE MEXICO,
Project Period:	2005/05/01-2010/04/30	

DESCRIPTION (provided by applicant): Leishmania is a parasitic protozoan (order Kinetoplastida) that causes a spectrum of disease ranging from asymptomatic to lethal, resulting in widespread human suffering and death. LmjF presents atypical mechanisms of gene expression, since transcription seems to initiate in only a few regions per chromosome, generating long polycistronic transcripts that are processed by trans-splicing to produce mature mRNAs. Little is known in kinetoplastids about transcription by RNA Polymerase III (Pol III), which transcribes several conserved and abundant small RNAs (such as tRNAs, 5S rRNAs and snRNAs) that play critical roles in cell metabolism. Our main objective is to characterize Pol III promoters and transcriptional complexes in Leishmania major Friedlin (LmjF), whose genome sequence has been recently completed. The specific hypothesis is that Pol III promoters and transcription factors in LmjF (and other kinetoplastids) differ considerably from those present on other eukaryotes. The specific aims are to: 1. Analyze transcription of Pol III genes in LmjF. Transcription start sites will be mapped by 5'-RACE, and termination sites localized by RT-PCR with poly(A)-tailed RNA. Nuclear run-on analysis will be performed with single-stranded DNA fragments spanning coding and intergenic regions. Promoter activity will be tested by transient-transfection studies. 2. Examine the DNA-protein interactions between the Pol III promoters and the transcription machinery. DNA-protein interactions will be analyzed by electrophoretic mobility shift assays. DNase I footprinting assays will be carried out to identify the specific DNA sequences that interact with the Pol III complex. 3. Identify the protein components of the Pol III complex in LmjF. The tandem affinity purification (TAP-tag) method will be used to purify Pol III transcriptional complexes. The protein components in these complexes will be identified by mass-spectrometry analysis.

Grant:	1R01TW007305-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	MWAPASA, VICTOR	PHD
Title:	Iron supplementation in HIV-infected pregnant women	
Institution:	UNIVERSITY OF MALAWI	CHICHIRI, BLANTYRE 3,
Project Period:	2005/03/15-2009/09/15	

DESCRIPTION (provided by applicant): Anemia is a major health problem in sub-Saharan Africa affecting 35-75% of pregnant women and is an important cause of maternal morbidity and mortality, fetal loss and low birth weight. As part of a strategy to prevent anemia and its adverse effects, the World Health Organization recommends routine use of iron supplementation in all pregnant women living in areas with high prevalence of iron-deficiency. However, there is little evidence showing that this intervention is effective in HIV-infected pregnant women. The major hypotheses in this study are that iron supplementation in HIV-infected pregnant women 1. is ineffective at preventing anemia 2. increases the risk and density of malaria infection 3. leads to increased deposition of iron in the bone marrow 4. increases HIV viral load. Currently, it would be considered unethical to test these hypotheses in a placebo-controlled randomized trial due to the absence of evidence from prior observational studies and the fact that iron supplementation is standard practice. Thus, a cross-sectional study of third trimester HIV-infected pregnant Malawian women will be conducted, in the third trimester, to compare between women who receive iron supplementation and those who do not, the prevalence of maternal anemia, the prevalence and density of malaria parasitemia, concentrations of ferritin, serum Transferrin Receptors (sTFR) and HIV-1 RNA. The correlation between duration of iron supplementation and these outcomes will also be assessed. Results from this study could form the basis for conducting a placebocontrolled randomized clinical trial assessing the detrimental or beneficial effects of iron supplementation in HIV-infected pregnant women or could lead to modifications of the current anti-anemia interventions in HIVinfected pregnant women.

Grant:	5R01TW006672-02	
Program Director:	PRIMACK, ARON	
Principal Investigator:	NAKKU-JOLOBA, EDITH	PHD
Title:	Seroprevallence and incidence of genital herpes in Ugan*	
Institution:	NEW MULAGO HOSPITAL	KAMPALA,
Project Period:	2003/09/30-2008/03/31	

DESCRIPTION (provided by applicant): Prevalence of herpes simplex type 1 and 2 virus (HSV-1 and 2) infection is high worldwide and is highest in developing countries like Uganda. International and local health organizations have called for studies to characterize genital herpes epidemiology in sub-Saharan Africa. Population estimates are needed for policy, for planning interventions, for valid measures of the effect of interventions and for research on new therapies and potential vaccines. The overall goal of this study is to determine the burden of infection and assess the modifiable risk factors associated with Herpes simplex types 1 and 2 infection in Kampala, Uganda with an aim of prevention of spread and relief of those who suffer with genital herpes. The proposed study will aim i) To estimate the age and sex specific prevalence of Herpes simplex type 1 and 2. ii). To estimate the incidence of Herpes simplex type 1 and 2 in an inception cohort of HSV-2 negative persons in an urban population in Uganda and iii) to identify modifiable risk factors associated with Herpes simplex types 1 and 2 prevalence and incidence in this population. The proposed study will be a two-stage stratified random population sample survey of female and male participants 15 to 65 years old in Kawempe division of Kampala District. To estimate prevalence of HSV-1 and 2, a cross-sectional serological survey at baseline will be done using type specific ELISA tests for herpes simplex type 1 and 2. Incidence will be assessed in an inception cohort of HSV-2 negative persons by 6 monthly testing for HSV-2. Risk factors for genital herpes will be assessed using a standardized questionnaire to collect information on age, sociodemographic characteristics, sexual behavior, sexual partner characteristics such as age differentials, and HIV infection status. Incidence densities and relative risks will be calculated from new HSV-2 infection and risk factors that predispose to HSV-2 incidence such as age, sex, (gender), sexual behavior, and HIV infection analyzed in a Cox proportional hazards model. By conducting a population study in an urban area in a country where rural studies show high prevalence we will describe the epidemiology genital herpes, gaining new knowledge about genital herpes in urban Uganda and highlighting the modifiable risk factors which can be targeted for effective interventions.

Grant:	1R01TW007303-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	PEDREIRA, JOICE N	PHD
Title:	Transmission of Drug-Resistant S. pneumoniae in Brazil	
Institution:	FEDERAL UNIVERSITY OF BAHIA	SALVADOR, BAHIA,
Project Period:	2005/04/01-2010/03/31	

DESCRIPTION (provided by applicant): Pneumococcal disease is a leading cause of mortality and morbidity worldwide. The public health consequences have become ever more urgent due to the global emergence of drug resistant S. pneumoniae. This phenomenon appears to be due to the spread of a limited number of clones and serotypes and raises questions whether 1) S. pneumoniae clones emerge because they are drug-resistant and became predominant clones through antibiotic selective pressure; or 2) drug-resistant clones emerge because of their intrinsic virulence characteristics such as the pathogen's ability to induce persistent nasopharyngeal carriage or invade the host following colonization. These epidemiological questions have important implications for the potential use in developing countries of conjugate pneumococcal vaccines and programs to control the empiric use of antibiotics. However, no studies have addressed these questions in Latin America and other regions in the developing world. We propose a community-based study of invasive pneumococcal disease and nasopharyngeal colonization in Salvador, a city of 2.6 million inhabitants in Northeast Brazil. Since 1996, we have established at Fiocruz a continuous surveillance for pneumococcal meningitis and recently implemented the field site infrastructure to conduct longitudinal community-based studies. We therefore have an opportunity to obtain information on pneumococcal disease burden in Brazil and study its natural history. We propose a community-based study that aims to: 1) Measure the burden of invasive pneumococococcal disease in children from Salvador, Brazil and determine the clonal composition of S. pneumoniae strains that cause invasive disease. 2) Determine whether the ability of S. pneumoniae to produce nasopharyngeal carriage and invasive disease following colonization is influenced by the its genotype, serotype or drug resistance status.

Grant: 5R01TW006187-03

Program Director: PRIMACK, ARON

Principal Investigator: PUTHANAKIT, THANYAWEE MD

Title: Effect of the HIV epidemic on children in Thailand

Institution: CHIANG MAI UNIVERSITY CHIANG MAI,

Project Period: 2002/09/24-2007/06/30

DESCRIPTION (provided by applicant) By the end of 1999, UNAIDS estimated that the number of children living with HIV/AIDS in hail and was 13,900. Antiretroviral treatment has not yet been implemented. Five-year survival from a limited number of HIV-infected children in Thailand was less than 30%, in contrast to 75% from the US cohort before the era of HAART. The natural history from a large cohort of HIV infected children is essential as baseline information in order to evaluate intervention including antiretroviral treatment. Since 2000, an extensive perinatal HIV prevention program has been implemented throughout Thailand. The HIV perinatal transmission rate is currently approximately 10% The outcome of children born to HIV-infected mothers, both infected and uninfected children, in terms of behavioral and psychosocial aspects are important to identify their special needs. Overall goal of this study is to characterize the natural history of children affected by HIV/AIDS epidemic in Thailand. The comprehensive understanding of natural history in this special population will lead to development of culturally and medically appropriate interventions to improve their quality of life. The specific aims of this proposal are (1) to characterize the natural history of HIV- infected children in terms of their overall survival and survival after the development of AIDS (2) to compare the natural history of HIV-infected children before and after Pneumocystis carinii prophylaxis has been implemented in 1996. We propose to examine a retrospective cohort of 940 HIV-infected children under medical care of the Department of Pediatrics, Chiang Mai University between 1989-2001 to address specific aims 1 and 2 (3) to characterize the psychosocial problems and needs of school-aged children born to HIV-infected mothers, both infected and uninfected children (4) to characterize the behavioral outcome of school-aged children born to HIV-infected mothers, both infected and uninfected children. We propose to perform a prospective cohort study of school-aged children born to HIV infected mothers at Chiang Mai University.

Grant: 5R01TW006195-03

Program Director: PRIMACK, ARON

Principal Investigator: RAMAKRISHNA, GAYATRI PHD

Title: Functioning of K-ras in lung type II epithelial cells

Institution: CTR FOR DNA FINGERPRINTING/DIAGNOSTICS ADHRA PRADESH,

Project Period: 2002/09/18-2007/06/30

DESCRIPTION (provided by applicant) K-ras is an important oncogene found to be mutated in almost 30% in the lung adenocarcinomas which has high incidence in countries like India and United States. The ras encodes for a 21kD protein, which is a crucial growth regulator of cells. Mutations in the hot spot codon of ras viz; codon 12, 13 and 61 have been frequently reported in many human and animal lung cancer. The knowledge is pretty limiting regarding functioning of K-ras p21 in lung epithelium. Therefore the goal of this study is to understand the mechanism of action of K-ras p21 functioning in normal growth and to see how its functioning differs following mutation leading to tumor development. We hypothesize that specific types of activating point mutations in K-ras oncogene can confer different growth advantages to the cells harboring it by turning on different downstream effector proteins (both quantitative and qualitative) involved in signaling. In this regard we plan to use both mouse (E10) and human (HPL1D) lung type II epithelial cells which are the target cells giving arise to adenocarcinomas. To eliminate ras independent gene expression between cell lines we will prepare tetracycline K-ras inducible constructs and transfect them into El0 and HPL1D cells. Following are the main objectives: (1) to analyze growth, cell cycle distribution and transforming efficiencies of the mouse and human lung epithelial cell lines containing different types of transfected inducible K-ras viz., wild type, mutants in codon 12,13 & 61, (2) to check for differential/preferential activation or crosstalks of Raf-MAPK and PI3-K-AKT pathway in the K-ras inducible cells (3) to identify targets of wild type and mutant K-ras by comparing the global gene expression profiles using membrane arrays. This kind of an approach will help delineate functioning of normal K-ras and also provide insights into functional consequences of specific mutations in ras and hence efforts can be directed towards molecular targeting for prevention and therapy.

Grant: 1R01TW007260-01

Program Director: PRIMACK, ARON

Principal Investigator: RAN, MAOSHENG PHD

Title: Suicidal Behavior in Persons with Schizophrenia in China

Institution: UNIVERSITY OF HONG KONG POKFULAM,

Project Period: 2005/04/01-2010/03/31

DESCRIPTION (provided by applicant): This application from the University of Hong Kong's Hong Kong Jockey Club Centre for Suicide Research and Prevention proposes to clarify the risk and protective factors of suicidal behavior (suicide and suicide attempts) in a long-term follow-up study in a Chinese rural community-based sample of 510 individuals with schizophrenia. Major collaborative colleagues are from University of Rochester and Sichuan University (China). Suicide research and prevention for persons with schizophrenia are international public health priorities. The limited knowledge base poses a significant obstacle to the development of prevention programs. Few prospective long-term studies of persons with schizophrenia in rural community have been conducted to determine risk and protective factors of suicidal behavior, especially in China. Given the unique characteristics of suicide and the lack of systematic psychiatric registration which allows us to study the mortality and suicide of psychiatric patients in China, this special research project should be important to explore the risk and protective factors of suicide among persons with schizophrenia. The long-term goal of this research program is to decrease suicide rates in people with schizophrenia through developing and implementing prevention strategies that target the identified risk and protective factors. The aims of this study are, first, to examine risk and protective factors (demographic, symptoms, treatment, social support) of suicide attempts, second, to explore risk and protective factors (demographic, symptoms, treatment, social support) of suicide, thus, this study aims also to identify the difference between suicide and suicide attempts. A 11-year prospective cohort study will be conducted. This study is a combination of both a prospective and a retrospective study, and a combination of cohort and nested case control designs. The subjects of this study will include all people with schizophrenia (N=510), who live in six townships of Xinjin County as identified in our previous study in 1994. All subjects were over 15 years of age and met the ICD-10 diagnosis of schizophrenia. All the subjects and/or next-of-kin will be traced and interviewed in community. Information of demographic, clinical symptoms, treatment, and social support will be collected. Univariate/descriptive, bivariate comparison, and regression analysis will be used to analyze the data. Odds ratios will also be calculated for predictor variables. The major advantage of the study is reduction of the methodological problems most often encountered in the previous studies. The results of this study will be crucial for further mental health intervention and prevention of suicide among persons with schizophrenia.

Grant: 1R01TW006972-01A1

Program Director: PRIMACK, ARON

Principal Investigator: RANGSIN, RAM MD

Title: Risk Factors for HIV-1 infection Among Young Thai Men

Institution: PHRAMONGKUTKLAO COLLEGE OF MEDICINE BANGKOK,

Project Period: 2005/04/01-2010/03/31

DESCRIPTION (provided by applicant): The course of HIV-1 epidemic in Thailand has been decreased dramatically since its peak in the early 1990s. Although Thailand has had substantial success in HIV prevention efforts, close to 30,000 new infections continue to occur each year. Pattern of risk behavior may have been changed since the peak of the epidemic. Studies during the early phase of the epidemic found that more than 90% of HIV infected men reported having sex with commercial sex workers as the risk behavior while it was only 1% for IDU. HIV-1 prevalence in IDU population showed the stable high prevalence around 40-50% since 1989 including the latest round of the surveillance. Thailand has established HIV surveillance among -60,000 21-year-old military conscripts annually. It is believed to be the nationally representative sample of young Thai men. This ongoing total survey is helpful to be studied for the changes of risk behavioral pattern in this population. HCV infection is prevalence in Thailand. To date the information about risk factors for HCV infection in Thailand was still limited. HCV antibody was believed to be a good surrogate marker for IDU in high HCV prevalence counties including Thailand. The long term goal of this study is to characterize the recent risk behavior for HIV-1 infection and the relationship between HIV-1 and HCV infections among young Thai men. Specific aims are:1. To characterize the pattern of high risk behaviors for HIV-1 infection among young Thai men aged 18-21 years old during 2005-2008 according to geographic area and the changes of the risk behaviors over time 2. To characterize prevalence of HCV infection according to geographic area and related risk factors among HIV-1 positive and negative young Thai men aged 18-21 years old and to assess the independent association between HIV-1 and HCV infections during 2005- 2008. We propose a case control study of HIV-1 infected young men and their 1:4 controls matched on year of birth, district of residence, and type of conscription.

Grant:	5R01TW006215-03	
Program Director:	PRIMACK, ARON	
Principal Investigator:	RIBEIRO-FILHO, LEOPOLDO A	MD
Title:	Biomarkers for detection of bladder cancer	
Institution:	FEDERAL UNIVERSITY OF SAO PAULO	SAO PAULO,
Project Period:	2002/09/20-2007/06/30	

DESCRIPTION (provided by applicant) The main goal of this project is to investigate the whether inactivation of E-cadherin, Beta and gamma-catenins can be used as biomarkers for bladder cancer initiation / progression or metastasis. Also investigate the molecular mechanisms of inactivation of E-cadherin, Beta and gamma-catenins in bladder cancer through mutation / CpG methylation pathways. We will also investigate the functional role of the E-cadherin, Beta, and gamma catenins genes in bladder cancer. Specific Hypotheses: We hypothesize that inactivation of E-cadherin, Beta, and gamma catenins is associated with stage and grades of bladder cancer. The mechanisms of inactivation of the E-cadherin, Beta, and gamma catenins gene are through mutation/hypermethylation pathways. Transfection of E-cadherin, Beta and gamma catenins genes will suppress growth of bladder cancer cells. To test these hypotheses, we will pursue the following specific aims. Specific Aim # 1. To analyze gene and protein expression of E-cadherin, Beta, and gamma catenins in different stages and grades of bladder cancer. This specific aim is based on the hypothesis that inactivation of E-cadherin, Beta, and gamma catenins genes can be detected in early stages of bladder cancer and that the frequency of loss of these genes increases with progression of the cancer process. Under this specific aim, we will determine the gene and protein expression of E-cadherin, Beta, and gamma catenins in normal and different stages and grades of bladder cancer. RNA expression will be analyzed by RT-PCR (for screening) and northern blot (for quantification). Protein expression will be analyzed by immunohistochemistry (for localization) and western blotting (for quantification). Specific Aim # 2. To investigate the mechanisms of inactivation of E-cadherin, Beta, and gamma catenins genes in bladder cancer. This specific aim is based on the hypothesis that mutation / hypermethylation pathways are involved in inactivation of E-cadherin, Beta, and gamma catenins genes in bladder cancer. Under this specific aim, we will first determine the mutation and CpG methylation of E-cadherin, Beta, and gamma catenins genes in different stages and grades of bladder cancer. CpG methylation will be analyzed by sodium bisulfite methylation techniques and confirm by direct DNA sequencing. Specific Aim # 3. To investigate the functional role of E-cadherin, Beta, and gamma catenins genes in bladder carcinogenesis. Under this specific aim, we will test the hypothesis that transfection of the E-cadherin, Beta, and gamma catenins genes in dominant-negative bladder cancer cells can suppress in vitro growth. Under this specific aim, we will transfect these genes and assess their in vitro growth and in vitro invasion assays. Accomplishment of these experiments will provide us with better biomarkers for detection of bladder cancer

Grant: 5R01TW006644-03

Program Director: PRIMACK, ARON

Principal Investigator: ROSENZWEIG, SERGIO MD

Title: Recycling of IFNgR2 modulates IFNg responsiveness

Institution: HOSPITAL DE PEDIATRIA J.P. GARRAHAN BUENOS AIRES,

Project Period: 2003/09/24-2006/03/31

DESCRIPTION (provided by applicant): The aim of our project is to precisely define the interferon gamma receptor (IFNgammaR) 2 recycling domain and the biologic effects of IFNgammaR2 modulation. Human disease and animal models show a broad and diverse spectrum of clinical phenotypes associated with differential IFNgamma receptor display and responsiveness. Increased susceptibility to infections, predominantly mycobacteria, but also including bacteria, virus and fungi; autoimmune disease pathogenesis; and tumor generation and control are all conditions associated with differential IFNgamma responsiveness and IFNgamma receptor display. The IFNgammaR complex is composed of four molecules, two IFNgR1 and two IFNgR2. After binding the IFNgammaR complex, IFNgamma triggers a broad spectrum of biological effects. While the IFNgammaR1 is constitutively expressed on all nucleated cells, IFNgammaR2 membrane display is quite limited and tightly regulated, creating a bottleneck in IFNgamma responsiveness. Several groups have hypothesized the existence of a recycling domain in IFNgammaR2, similar to what has been demonstrated in IFNgammaRI. We have identified the discrete amino acids in the intracellular domain of IFNgammaR2 that mediate its recycling, and lead to plasma membrane over-accumulation when altered. Truncation of the receptor immediately upstream of the recycling domain, or deletion or substitution of the sequence of the amino acids involved in the recycling domain, have enabled us to create dominant negative and dominant gain of function IFNgammaR2 mutants, respectively. These results are the first physical evidence of the existence of an IFNgammaR2 recycling domain and the first demonstration of dominant negative, as well as dominant gain of function mutations in IFNgammaR2. This research project is designed to understand how modulation of the IFNgammaR2 recycling domain affects IFNgamma signaling, IFNgamma receptor trafficking, IFNgamma mediated apoptosis, and immune-mediated cytotoxicity towards cells expressing IFNgammaR2 mutants. We expect that by exploring the fate of IFNgammaR2, the molecule described as the bottleneck in IFNgamma responsiveness, we will expand our knowledge of the immune system, the way it controls external infectious challenges, the immune mediated generation of certain diseases, and some of the mechanisms of the immune control of cancer.

Grant:	5R01AG023217-02	
Program Director:		
Principal Investigator:	RUTAREMWA, GIDEON	PHD
Title:	MORTALITY DIFFERENTIALS IN UGANDA IN THE ERA OF HIV/AIDS	
Institution:	MAKERERE UNIVERSITY	KAMPALA,
Project Period:	2003/09/15-2006/08/31	

DESCRIPTION (provided by applicant) This project proposes to analyze mortality correlates in Uganda during the HIV/AIDS period. The project builds on prior work to analyze the levels, trends and patterns of - childhood mortality, and extends to examine adult mortality and maternal health aspects. The projects seek to take advantage of all existing survey and census data as well as the improved demographic methods to examine an important health and demographic dynamic. This project seeks to contribute to knowledge and expand understanding of the changing Ugandan health and morbidity environment in the face of the HIV/AIDS epidemic. The proposed study will provide empirical analysis of the demographic dimensions of one of the main outcomes of health during the 20 years since AIDS was first reported in Uganda.

Grant:	1R01TW007252-01
Program Director:	PRIMACK, ARON
Principal Investigator:	SAGHAYAM, SUNEETA PHD
Title:	HAART associated body shape & metabolic changes in India
Institution:	YRG CENTRE FOR AIDS RESEARCH & EDUCATION CHENNAI, TN,
Project Period:	2005/04/01-2010/03/31

DESCRIPTION (provided by applicant): Objective: To evaluate the initial response to EFV-based HAART and the evolution of those changes over time on HAART in HIV infected previously ART-naive patients in South India. Comparison with a matched, untreated group will allow us to differentiate the role of antiretrovirals versus the natural progression of HIV infection on the nutritional status, metabolic, body shape, body composition and bone parameters. These data have not been previously reported from Asia. Specific Aim I: In the treatment group, a)To describe the nutritional, body shape and metabolic responses to the initiation of therapy (EFV-HAART) between baseline and 6 months; b)To describe the evolution of nutritional, body shape and metabolic response to continuous HAART therapy between 6-36 months Specific Aim II: In the untreated group, to describe the evolution of body composition and lipid changes with the natural progression of HIV infection (subjects must maintain CD4 between 300-500, if GD4 drops <200, therapy will be initiated and subjects will be withdrawn from the study). Study design: A 36 months prospective longitudinal study where study subjects recruited by HPTN study #052 with CD4 between 300 - 500 are randomized to either receive HAART treatment or remain untreated. All subjects in HPTN 052 will be asked to provide consent to enroll in this study in which they will be followed every 6 months for 3 years to observe body shape and metabolic changes Methods: Body shape and body composition changes will be assessed using anthropometry, BIA (every 6 months) and DEXA (yearly). Metabolic changes will be evaluated every 6 months by fasting lipids, insulin, glucose and 2hr glucose (yearly). Fasting lactate and C-reactive protein will also be measured every 6 months.

Grant:	5R01TW006223-03
Program Director:	PRIMACK, ARON
Principal Investigator:	SAPIRO, ROSSANA MD
Title:	CHARACTERIZATION OF FLAGELLAR PROTEINS INVOLVED IN SPER*
Institution:	UNIVERSITY OF THE REPUBLIC MONTEVIDEO,
Project Period:	2002/09/18-2007/06/30

DESCRIPTION (provided by applicant) Sperm must have purposeful forward motion following deposition in the female reproductive tract in order to fertilize ovulated eggs. The factors that control the sperm flagellar power stroke and waveform are poorly understood. Spag6, a protein containing eight armadillo repeats, a protein interaction motife, is the murine orthologue of Chlamydomonas PF16, a central apparatus protein required for algae flagellar function. Mice lacking Spag6 are infertile due to a severe sperm motility defect, resulting in part from disruption of the flagellar axoneme architecture. This model will be used to identify proteins that interact with Spag6 and thus expand the catalogue of the mammalian axonemal proteins that are essential for flagellar structure and function. Using two dimensional gel electrophoresis and surface-enhanced laser desorption/ionization mass spectrometry, the proteome of Spag6-deficient sperm will be characterized and compared with wild-type mouse sperm to identify missing proteins. The missing proteins will be characterized and their cDNAs cloned for further documentation of interaction with Spag6 using yeast two-hybrid and pull-down assays and immunocytochemical co-localization. The domains of Spag6 that mediate protein-protein interactions will be defined using yeast two-hybrid and other assays. The proteome of human sperm with motility and ultrastructural defects that mirror those of the Spag6-deficient mouse will be examined to screen for humans with SPAG6 deficiency. The knowledge gained from this research will provide a molecular framework for understanding sperm motility defects that cause male infertility and possibly offer new avenues for contraception through the disruption of purposeful sperm motion.

Grant:	5R01TW006185-03
Program Director:	PRIMACK, ARON
Principal Investigator:	SEN, RANJAN PHD
Title:	Transcription termination and antitermination in E.coli
Institution:	CTR FOR DNA HYDERABAD, FINGERPRINTING/DIAGNOSTICS
Project Period:	2002/09/18-2007/06/30

DESCRIPTION (provided by applicant) Transcription is key to all the cellular processes and RNA polymerase (RNAP), the enzyme responsible for transcription, is an attractive drug target in different microbial pathogens. At a given time most of the RNAP molecules are engaged in mRNA synthesis and rapid turn over, which involves two crucial steps in transcription, namely elongation and termination. So, ideally drug target should be the DNA-bound RNAP molecules engaged in these two modes, rather than their free form in cytosol. Long term goal of this project is to understand the mechanistic aspects of elongation, termination and as well as antitermination steps of the transcription process, so that a rational drug designing will be possible in future. Major focus will be to elucidate the active site dynamics of RNAP and intricate protein-DNA-RNA interactions during these steps. N-mediated antitermination system from lamdoid phage, which involves E.Coli RNAP, is an ideal system to study the protein-DNA-RNA interactions in the transcription elongation complex and as well as to understand the mechanism of termination/antitermination processes. In vivo studies indicate that shiga-toxin bearing lamdoid phage, H19B, requires a phage factor N and the host factor NusA to modify the elongation complex and achieve antitermination. Therefore, this antitermination complex is much simpler for biochemical and structural studies. Interactions in this modified elongation complex will be characterized by mutagenesis, Fe-BABE cleavage and fluorescence spectroscopy. 3D localization of N-binding surface on RNA polymerase will be obtained from homology modeling based on Taq RNA polymerase and Yeast RNA Pol II crystal structures together with the data obtained from the experiments stated above. In parallel studies, the active-site dynamics of RNAP in response to different DNA sequences, nascent RNA structure and trans factors (like N protein etc.), will be studied experimentally by using, chemical cleavage, foot printing, cross linking, and fluorescence spectroscopy. Computational methods, such as molecular dynamics simulations will also be used to predict the domain movement around the active site, which will be used to design mutations in specific domains and find its interacting partners by suppressor genetics. Understanding of the active site dynamics will lay the foundation for rational drug design in future.

Grant:	5R01TW006622-02	
Program Director:	PRIMACK, ARON	
Principal Investigator:	TERRON, JOSE A	BOTH
Title:	Brain serotonin and angiotensin II systems in migraine	
Institution:	CINVESTAV-IPN	MEXICO CITY,
Project Period:	2003/09/30-2008/03/31	

DESCRIPTION (provided by applicant) Long-term objectives. The brain serotonin (5-HT) system plays an important role in cerebrovascular and neuroendocrine control. These systems have been implicated in migraine. Migraine is a low 5-HT syndrome and attacks may be triggered by a massive release of 5-HT acting on sensitized receptors. This proposal will elucidate the association between the phenomena of decreased 5-HT neurotransmission and altered cerebrovascular and neuroendocrine responsiveness. Focus will be on 5-HT receptors recently implicated in migraine pathogenesis and/or prophylactic treatment (5-HT1A, 5-HTT, 5-HT2s and 5-HT2c). As a key activator of the hypothalamic-pituitary-adrenal (HPA) axis, the role of the brain angiotensin II (Ang II) system will be addressed. The proposal intends to shed light into the pathophysiological mechanisms of migraine, and the mechanism of action of migraine prophylactic 5-HT and Ang II drugs. Specific aims. The following hypotheses will be challenged: 1) A decreased 5-HT transmission in the brain will cause sensitization and/or up-regulation of 5-HT receptor subtypes in the cerebral vasculature and the HPA axis; treatment with a migraine prophylactic compound that target these receptors will restore 5-HT receptor function and/or expression. This may be a useful animal model for drug screening in migraine prophylaxis. 2) The response to stress, which involves sequential activation of the brain Ang II and the HPA systems, will lead to decreased brain 5-HT levels, up-regulation of 5-HT receptors, and/or amplified neuroendocrine and cerebrovascular responses to 5-HT receptor activation; treatment with an inhibitor of Ang II synthesis will restore serotonergic function. Design. 1) Cerebrovascular and neuroendocrine responses to 5-HT agonists, and expression of 5-HT receptors in the cerebral vasculature and the HPA axis, will be determined in control and 5-HT-depleted Wistar rats. It will be determined whether chronic treatment with a migraine prophylactic 5-HT antagonist restore 5-HT receptor function and/or expression. 2) Brain 5-HT content, expression of 5-HT receptors in the HPA axis, and neuroendocrine and cerebrovascular responses will be determined in control and stressed (acute and chronic isolation and restraint) Wistar rats. Reversal of stress-induced changes in these variables will be attempted by chronic treatment with the angiotensin-converting enzyme inhibitor, lisinopril (i.e. a migraine prophylactic agent). In vivo cerebrovascular reactivity will be assessed by laser- Doppler flowmetry (cortical blood flow) and the 4-iodo-[N-methyl-14C]-antipyrine method (regional cerebral blood flow). In vitro cerebrovascular reactivity will be analyzed with an arteriographic chamber system. The hormonal response (ACTH, corticosterone and prolactin) will be measured by radioimmuno assay in blood samples and 5-HT receptor expression will be determined by quantitative receptor autoradiography in tissue sections. 5-HT content will be measured by HPLC in brain homogenates.

Grant:	5R01TW006201-03
Program Director:	PRIMACK, ARON
Principal Investigator:	THIENPRASERT, ALICE PHD
Title:	Omega-3 Fats, Immune Functions and Behavioral Disorders
Institution:	SILPAKORN UNIVERSITY NAKHON PATHOM,
Project Period:	2002/09/23-2007/06/30

DESCRIPTION (provided by applicant) Childhood illnesses and behavioral disorders are major health problems in developing countries. This proposal develops a potential approach to solving these global health problems based on a specific nutritional approach that is both conservative and economical. There will be three aims in this large (n=1,200) double blind placebo-controlled, intervention trial of omega-3 fatty acid supplementation of school lunch milk for 8 months. Aim 1: determine if supplementation reduces the incidence or duration of common childhood illnesses. Aim 2: determine if supplementation improves clinically significant behavioral problems: depression and aggression. Aim 3: determine if supplementation improves academic performance as a direct effect on brain function or secondary to reductions of illness or improvements in behaviors. All children enrolled in the study will receive the active agent or placebo. Sub-cohorts of children will be identified for the specific examination of the effects on childhood illnesses, children with behavioral problems and in healthy children. This approach will also allow an examination of the interaction between the behavioral disorders, immunological function and resulting impacts on academic performance. A sub-cohort of children, those who contract an illness, will be intensively examined by a research nurse and physician, if necessary, to determine if there are differences in the severity and duration of illnesses. The sub-cohort of children with clinically significant behavioral problems will be identified using the Child Behavior Checklist and the Thai depression inventory. In this sub-cohort, sensitive and specific behavioral measures of aggression will be performed to assess the efficacy of the supplementation. The Child Behavior Checklist and Thai depression inventory assessments will also serve to estimate the prevalence of these disorders among Thai school children. Finally, the interrelationships between the presence of childhood illnesses, behavioral disorders and academic performance will be examined.

Grant:	1R01TW006990-01	
Program Director:	PRIMACK, ARON	
Principal Investigator:	UUSKULA, ANNELI	MD
Title:	Screening for STDs using home sampling in Estonia	
Institution:	UNIVERSITY OF TARTU	TARTU 50090 ESTONIA,
Project Period:	2004/07/01-2007/06/30	

DESCRIPTION (provided by applicant): Background: During recent decades there have been considerable developments in the field of sexually transmitted diseases (STDs). These changes have been driven largely by the HIV/AIDS epidemic, but also by an increased recognition of the range and severity of complications and sequelae linked to other STDs. Unfortunately, the prevalence and distribution of STDs within the Estonian population are poorly understood. Objective: To assess the acceptability and feasibility of home sampling as a population-based outreach screening program for STDs in a country of post-soviet transitional economy; and to determine the revalence of and risk factors for Chlamydia trachomatis and Neisseria gonorrhoeae infections among the study population. Methods, design: We will perform a cross-sectional study, based on a probability sample, of residents of Tartu County; 1,690 persons (845 women and 845 men) aged 18-39 will be randomly sampled from the Estonian Population Registry. The study activities include an outreach-screening program utilizing home sampling of Chlamydia trachomatis and Neisseria gonorrhoeae, together with a written survey. Those selected from the population registry will receive a mailing consisting of an explanatory letter, a urine sample container, a study survey, and a prepaid return envelope. Participants will be re-screened after 6 months. The main outcome measures will be the response rate and prevalence of infections, as measured by the percentage of specimens testing positive for gonococcal and/or genital chlamydiai infection by polymerase chain reaction. An alternative prevalence estimate will be derived from survey respondents'answers to questions asking whether they have been diagnosed as having gonorrhea or chlamydia in the 12 months prior to the survey. This information will allow us to identify STD infected individuals, and to develop selective screening criteria to be used in general population studies and screening programs in Estonia.

Grant: 1R01TW007271-01

Program Director: PRIMACK, ARON

Principal Investigator: VALASEK, LEOS PHD

Title: Regulation of eukaryotic translation initiation

Institution: CZECHOSLOVAK ACADEMY OF SCIENCES PRAGUE,

Project Period: 2005/05/01-2010/04/30

DESCRIPTION (provided by applicant): Translation initiation is a multiple-step process involving a large number of eukaryotic initiation factors (eIFs) that ultimately orchestrate assembly of the Met-tRNAiMet base-paired with the AUG start codon of mRNA on the 80S ribosome. Our long-term goal is to elucidate the regulation of this process as it plays a critical role in development, differentiation, cell cycle progression, cell growth, and apoptosis and its deregulation results in a loss of cell cycle control and malignant transformation of cells. Of all the initiation factors, eIF3 is particularly intriguing because it stimulates multiple steps in the pathway such as binding of Met-tRNAiMet and mRNA to the 40S ribosome. The specific hypothesis is that yeast eIF3 promotes 40S-binding of eIFs 1, 2, and 5, that were previously implicated in the AUG recognition process, and thus co-regulates the process during which the 40S ribosome scans the 5'UTR of mRNA until it encounters the start AUG codon. We base that hypothesis on the observations that A) yeast eIF3 forms a multifactor complex (MFC) with eIFs 1, 5 and Met-tRNAiMet-eIF2-GTP ternary complex (TC) that can exist free of ribosomes, B) several potential contacts that we found between eIF3 and the 40S ribosome seem to be important for the MFC delivery to the ribosome, and C) clustered-alanine mutations in NIP1 subunit of eIF3 appear to influence 43S complex formation and stringency of AUG recognition. To address this hypothesis: 1) We will mutate the eIF3-40S binding sites and analyze their physiological importance using techniques of yeast genetics and biochemistry, e.g. in vitro binding assays, in vivo affinity chromatography, HCHO cross-linking and fractionation of extracts by sucrose gradients sedimentation; and 2) attempt to identify additional MFC contacts with 40S. 3) We will conduct a site-directed mutagenesis of the selected segments of the NIP1 subunit of eIF3 that mediates interactions with eIFs 1, 2, and 5 followed by thorough analysis of mutant phenotypes indicating relaxed stringency of AUG selection and defects in TC recruitment to 40S.

Grant: 1R01TW006664-01

Program Director: PRIMACK, ARON

Principal Investigator: VAZQUEZ-PRADO, JOSE PHD

Title: MOLECULAR MECHANISMS IN POLARIZED CELL MIGRATION

Institution: CINVESTAV-IPN MEXICO CITY,

Project Period: 2004/02/01-2009/01/31

Revised Abstract: DESCRIPTION (provided by applicant): Polarized cell migration (PCM) is key for cell defense against infections, wound healing, axonal growth, embryonic development, tumor cell metastasis and angiogenesis. Our hypothesis postulates that P-REX1, an exchange factor for Rac, establishes critical protein-protein interactions with receptors, G proteins and novel elements participating in PCM. Our specific aims are: 1) To define molecular links leading to the activation of Rac by G proteins. 2) To determine if P-REX1, identified as a Rac activator responding to Gbetagamma and PI3K (Welch et al, 2002, Cell 108:809), establishes protein interactions relevant for PCM. 3) To determine the role of G betagamma- and P-REXl-interacting proteins in the activity of Rac and PCM. Our studies consider the modular architecture exhibited by P-REX1, which contains two DEP and two PDZ domains, suggestive of modulation by direct protein-protein interactions. Our long term goal is to understand the molecular aspects of signal transduction required for PCM of endothelial cells and to identify molecular antiangiogenic tools. The role of Gbetagamma in PCM will be monitored in the presence of phosducin-like protein- and GRK2- derived peptides. P-REX1 deletion mutants lacking the different structural domains will be prepared to identify the structural domains in P-REX1 recognized by Gbetagamma and PI3K and to reveal their role in the activation of Rac and PCM. To identify novel elements able to modulate endothelial cell migration, Gbetagamma- and P-REXl interacting proteins will be cloned by yeast two hybrid and, in parallel, will be identified by proteomic approaches. It will be determined if CXCR1 and CXCR2 GPCRs containing PDZ-interacting motives in their carboxyl terminal domain are able to establish stable interactions with P-REX1. CXCR4 that does not contain that motif will be used as a control. Human HEK293T cells will be the model to study molecular interactions. Those cells will be transfected with the diverse DNA constructs. Recombinant molecules will be expressed fused to GST, EGFP, Myc or HA tags that will facilitate their study. Endothelial cells will be used to determine the role of Gbetagamma, P-REX1 and their interacting proteins, on the activation of Rac and polarized migration responding to the activation of angiogenic G protein coupled receptors. Discovery of molecular elements that might impede unwanted endothelial cell migration will provide elements for the design of antiangiogenic treatments.

Grant: 1R01TW007294-01

Program Director: PRIMACK, ARON

Principal Investigator: WANG, JINZHONG PHD

Title: Interferon and Kaposi's sarcoma herpesvirus interaction

Institution: NANKAI UNIVERSITY TIANJIN,

Project Period: 2005/05/01-2010/04/30

DESCRIPTION (provided by applicant): Kaposi's sarcoma-associated herpesvirus (KSHV) also known as human herpesvirus-8 (HHV-8) is the etiologic agent of Kaposi's sarcoma (KS), the most common neoplasm in untreated HIV-1 infected individuals. In China where there is an increase in the number of HIV-1 infected individuals, it is likely that KS will also become a major problem in these patients as their disease progresses. KSHV infection goes through lytic and latent phases and viral lytic replication plays an essential role in the development of KS tumors. Our data suggests that innate immunity, through the interferon pathway, is involved in suppressing lytic viral replication. Our findings indicate that upon KSHV infection, the host responds by suppression of lytic gene expression through the interferon responding factor 7 (IRF-7). IRF-7 competes for promoter binding sites with an essential viral regulatory protein known as RTA (replication and transcription activator) which alone is sufficient to initiate lytic replication by activating downstream lytic genes. Moreover, it is likely that post-translational modification and activation of IRF-7, such as phosphorylation or sumoylation may also be involved in the repression of RTA. Our overall objective for the proposed study is to further understand how IRF-7 antagonizes RTA activation pathways, whether activation and modification of IRF-7 are required, and to identify and characterize the viral and cellular factors involved. We hypothesize that in KSHV infected cells, newly activated IRF-7 competes with the viral RTA to prevent RTA's binding and activation of viral lytic gene expression, and thereby inhibits viral replication. To substantiate this hypothesis, the following aims are proposed: Aim 1: to characterize the molecular interplay between IRF-7 and RTA. Aim 2: to understand how IRF-7 is stimulated, modified and involved in repression of lytic viral replication. Aim 3: To investigate the role of IRF-7 in the regulation of KSHV lytic replication during infection. A more complete understanding of the mechanisms that control and suppress viral replication could lead to development of preventive strategies against KS in HIV-1 infected individuals.

Grant: 5R01TW006193-02

Program Director: PRIMACK, ARON

Principal Investigator: WONG-CHEW, ROSA M MD

Title: Evaluation of the aerosol measles vaccine in children

Institution: FUNDACION MEXICANA PARA LA SALUD, A.C. MEXICO,

Project Period: 2003/09/30-2008/03/31

DESCRIPTION (provided by applicant) The objective of this project is to evaluate the immune response to measles vaccine administered by aerosol to children. The specific aims are: 1) To evaluate measles vaccine by aerosol and subcutaneous route in children of 12, 9 and 6 months old. 2) To evaluate the effect of passive antibodies on the capacity of the aerosol measles vaccine to elicit a humeral and cellular response. 3) To evaluate the secretary IgA response to measles vaccine given by aerosol and subcutaneous route in children 12, 9 and 6 months old. 4) To evaluate the response to subcutaneous revaccination in children who were given aerosol for their first dose. 5) To compare the cellular responses of infants to bacterial and viral antigens according to the route of measles vaccine administration. Measles is still a problem of public health. Despite the availability of live measles vaccine, measles infections account for 10% of global mortality of all causes among children less than 5 years old. Measles is highly transmissible and outbreaks can still emerge. The aerosol measles vaccine could be helpful in mass vaccination, because it is easy to deliver and is well accepted by children and mothers. The Pan American Health Organization has targeted the year 2010 for measles eradication in the Americas. In addition to the potential benefits for immunogenicity, the mucosal delivery of measles vaccine may have practical advantages for measles eradication programs. This study is based on a very well established partnership between the National Autonomous University of Mexico, National Institute of Public Health of Mexico and Stanford University. We plan to enroll 630 children during a 5-year period. Children will be identified from birth records for Queretaro, Queretaro, Mexico. The eligibility criteria will be healthy children of 6, 9 and 12 months old. They will be randomized in a 1:1 ratio to receive measles vaccine by aerosol or subcutaneous route. Blood draws will be taken before vaccination and 12 weeks after immunization for Specific Aim 1 and 2. For Specific Aim 4 a subgroup of children (of each age cohort and each vaccine) will have a third blood draw 3 months after a booster with MMR at 12 or 15 months old (6 and 9 month old children will receive a booster at 12 months of age, and 12 month-old children will receive a booster at 15 months of age). For Specific Aim 5 another subgroup (of each age cohort and each vaccine) will have the 2 ndblood draw at 2 weeks and the 3'd blood draw at 12 weeks after immunization. For Specific Aim 3 another subgroup or children (of each age cohort and each vaccine) in addition to blood samples, saliva samples will be taken before vaccination and 4 weeks after immunization. Nurses will visit the children for 14 days after the vaccination to record any symptom. Cellular immunity, cytokine and measles specific IgA assays will be performed at the laboratory in Mexico City, plaque reduction neutralization assays will be performed at the National Institute of Public Health, Mexico.